

REMARKS

Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached page is captioned "Version with markings to show changes made."

Applicants reserve the right to prosecute non-elected subject matter in subsequent divisional applications.

I. Enablement rejection under 35 U.S.C. § 112, first paragraph

The rejection of claim 2 under the first paragraph of 35 U.S.C. § 112, because the specification allegedly does not provide an enabling disclosure commensurate in scope with the claimed invention, was maintained. In particular, the Office Action has objected to the recitation of polypeptide variants having at least 90% sequence identity to SEQ ID NO:1 or SEQ ID NO:2.

Claim 2 has been amended to recite "naturally-occurring" amino acid sequences. Support for this amendment is found in the specification, at, for example, p. 6, lines 9-12; p. 6, lines 24-30; and p. 7, lines 12-15. Since the recited naturally-occurring amino acid sequences are fully enabled by the specification, it is believed that this rejection should now be withdrawn.

II. Rejections under 35 U.S.C. § 101 and 35 U.S.C. § 112, first paragraph

Claims 1, 2, 21, 22, and 27-29 were rejected under 35 U.S.C. § 101 based on the allegation that the claimed invention is not supported by either a credible, substantial, and specific asserted utility or a well established utility. These claims were also rejected under 35 U.S.C. § 112, first paragraph, asserting that a person skilled in the art to would not know how to make and/or use the claimed invention. Applicants respectfully traverse these rejections.

Applicants' invention is directed, *inter alia*, to human prostate growth-associated membrane proteins PGAMP-1 and PGAMP-2, comprising the amino acid sequences of SEQ ID NO:1 and SEQ ID NO:2, respectively. These polypeptides have strong chemical and structural homology to rat heat-stable antigen CD4 (GI 1216498; SEQ ID NO:5), mouse apoptosis-associated tyrosine kinase (GI 2459993; SEQ ID NO:6), and human prostate specific antigen (GI

130989; SEQ ID NO:7). In particular, PGAMP-1 and rat heat-stable antigen CD4 share 21% identity, PGAMP-2 and a fragment of mouse apoptosis-associated tyrosine kinase share 17% identity, and PGAMP-2 and human prostate specific antigen share 18% identity. In addition:

1. "PGAMP-1 is 141 amino acids in length and has one potential casein kinase II phosphorylation site at residue S35; one potential protein kinase C phosphorylation site at residue S15; one potential tyrosine kinase phosphorylation site at residue Y110; three potential transmembrane regions between about residues I44 to P67, I81 to W102, and P117 to Q135; and has chemical similarity with CD44 antigen precursor. . . Northern analysis shows the expression of this sequence in various libraries, at least 72% of which are immortalized or cancerous and at least 18% of which involve immune response. Of particular note is the expression of PGAMP in cancerous or hyperplastic prostate (48%) or breast (7%); and in brain and adrenal gland." (Specification at page 14)
2. "PGAMP-2 is 410 amino acids in length and has a potential N-glycosylation site at residue N273; one potential cAMP- and cGMP-dependent protein kinase phosphorylation site at residue S355; one potential casein kinase II phosphorylation site at residue S274; seven potential protein kinase C phosphorylation sites at residues T118, S121, T131, S274, S311, S366, and S378; one potential tyrosine kinase phosphorylation site at residue Y21. In addition a hydropathy plot of PGAMP-2 predicts nine potential transmembrane regions between about residues L16 to Y31, P37 to V49, Q51 to Q73, V76 to L92, N101 to T118, F137 to F155, I165 to P182, R230 to W251, and T400 to V410; and a potential signal peptide sequence from M1 to S12. . . The three proteins [PGAMP-2, mouse apoptosis-associated tyrosine kinase, and human prostate specific antigen] also share six transmembrane regions and the potential signal peptide. In addition, PGAMP-2 and human PSA have rather similar isoelectric points, 8.7 and 7.5, respectively. . . Northern analysis shows the expression of this sequence in various libraries, at least 76% of which are immortalized or cancerous and at least 18% of which involve immune response. Of particular note is the expression of PGAMP-2 in cancerous or hyperplastic prostate (28%) and breast (10%); and in uterus, ovary, and colon." (Specification at pages 14 and 15)

The rejection of claims 1, 2, 21, 22, and 27-29 under 35 U.S.C §§ 101 and 112, first paragraph, is improper, as the claims have a patentable utility as set forth in the instant specification, and/or a utility well-known to one of ordinary skill in the art; and one of skill in the art would know how to make and/or use the claimed invention.

The claims were rejected under 35 U.S.C. §§ 101 and 112, first paragraph, based on the allegation that the claimed invention lacks patentable utility, and that one of skill in the art would not know how to make and/or use the claimed invention. The rejections allege in particular that "undue experimentation would be required to use the instantly claimed polypeptides," and "The credibility and the specificty [sic] of the asserted utility is undermined when the claimed

polypeptides have yet to be definitively characterized. The specification does not support the use of these claimed PGAMPs as selective markers for just prostate cancer or as compounds to be used in the treatment of prostate disorders and/or cancer." Applicants respectfully submit that these bases for rejection are improper, and in any case, there is a well-established utility for the claimed sequences, and indeed for all expressed sequences, that has not been considered.

The invention at issue includes polypeptide sequences expressed in human tissues, including reproductive, neuronal, and gastrointestinal tissues, and tissues associated with cancer and the immune response. As such, the claimed inventions have numerous practical, beneficial uses in toxicology testing, drug development, and the diagnosis of disease, none of which necessarily require detailed knowledge of how the polypeptides work. As a result of the benefits of these uses, the claimed inventions already enjoy significant commercial success.

Any of these uses meets the utility requirements of 35 U.S.C. § 101 and, derivatively, § 112, first paragraph. Under these sections of the Patent Act, the patent applicant need only show that the claimed invention is "practically useful," *Anderson v. Natta*, 480 F.2d 1392, 1397, 178 USPQ 458 (CCPA 1973) and confers a "specific benefit" on the public. *Brenner v. Manson*, 383 U.S. 519, 534-35, 148 USPQ 689 (1966). As discussed in a recent Court of Appeals for the Federal Circuit case, this threshold is not high:

An invention is "useful" under section 101 if it is capable of providing some identifiable benefit. See *Brenner v. Manson*, 383 U.S. 519, 534 [148 USPQ 689] (1966); *Brooktree Corp. v. Advanced Micro Devices, Inc.*, 977 F.2d 1555, 1571 [24 USPQ2d 1401] (Fed. Cir. 1992) ("to violate Section 101 the claimed device must be totally incapable of achieving a useful result"); *Fuller v. Berger*, 120 F. 274, 275 (7th Cir. 1903) (test for utility is whether invention "is incapable of serving any beneficial end").

Juicy Whip Inc. v. Orange Bang Inc., 51 USPQ2d 1700 (Fed. Cir. 1999). In *Stiftung v. Renishaw PLC*, 945 F.2d 1173, 1180, 20 USPQ2d 1094 (Fed. Cir. 1991) the United States Court of Appeal for the Federal Circuit explained:

An invention need not be the best or only way to accomplish a certain result, and it need only be useful to some extent and in certain applications: "[T]he fact that an invention has only limited utility and is only operable in certain applications is not grounds for finding lack of utility." *Envirotech Corp. v. Al George, Inc.*, 730 F.2d 753, 762, 221 USPQ 473, 480 (Fed. Cir. 1984).

If persons of ordinary skill in the art would understand that there is a "well-established" utility for the claimed invention, the threshold is met automatically and the applicant need not

make any showing to demonstrate utility. Manual of Patent Examination Procedure at § 706.03(a). Only if there is no "well-established" utility for the claimed invention must the applicant demonstrate the practical benefits of the invention. *Id.*

Once the patent applicant identifies a specific utility, the claimed invention is presumed to possess it. *In re Cortright*, 165 F.3d 1353, 1357, 49 USPQ2d 1464; *In re Brana*, 51 F.3d 1560, 1566; 34 USPQ2d 1436 (Fed. Cir. 1995). In that case the Patent Office bears the burden to demonstrate that a person of ordinary skill in the art would reasonably doubt that the asserted utility could be achieved by the claimed invention. *Ids.* To do so, the PTO must provide evidence or sound scientific reasoning. See *In re Langer*, 503 F.2d 1380, 1391-92, 183 USPQ 288 (CCPA 1974). If and only if the Patent Office makes such a showing, the burden shifts to the applicant to provide rebuttal evidence that would convince the person of ordinary skill that there is sufficient proof of utility. *Brana*, 51 F.3d at 1566. The applicant need only prove a "substantial likelihood" of utility; certainty is not required. *Brenner*, 383 U.S. at 532.

The rejections fail to demonstrate either that the Applicants' assertions of utility are legally insufficient or that a person of ordinary skill in the art would reasonably doubt that they could be achieved. For these reasons alone the rejections should be withdrawn.

There is, however, an additional, independent reason to overturn the rejections: to the extent the rejections are based on Revised Interim Utility Examination Guidelines (64 FR 71427, December 21, 1999), the final Utility Examination Guidelines (66 FR 1092, January 5, 2001), and/or the Revised Interim Utility Guidelines Training Materials (USPTO Website www.uspto.gov, March 1, 2000), the Guidelines and Training Materials are themselves inconsistent with the law. These inconsistencies are discussed separately below.

- A. Use in drug discovery as screening tools for identifying agonists and antagonists; as diagnostics for cancer and reproductive and immunological disorders; as controls (the polypeptides) or hybridization tools (the polynucleotides) for monitoring expression of said polypeptides and/or polynucleotides for monitoring disease progression; as well as to develop and monitor the activities of therapeutic agents, and in particular, for the well-known specific use in toxicological studies for new drug development, are sufficient utilities under 35 U.S.C. §§ 101 and 112, first paragraph.**

The claimed invention meets all of the necessary requirements for establishing a credible utility under the Patent Law: There is a "well-established" use for the claimed invention, there

are specific practical and beneficial uses for the invention, and those uses are substantial. Objective evidence, not considered by the Patent Office, further corroborates the credibility of the asserted utilities.

- i. **The use of human polynucleotides and their encoded polypeptides as tools for toxicology testing, drug discovery, and the diagnosis of disease, is "well-established."**

In recent years, scientists have developed important techniques for toxicology testing, drug development, and disease diagnosis. Many of these techniques rely on expression profiling, in which the expression of numerous genes is compared in two or more samples. Genes or gene fragments known to be expressed, such as the invention at issue, are tools essential to any technology that uses expression profiling. See, *e.g.*, Sandra Steiner and N. Leigh Anderson, Expression profiling in toxicology -- potentials and limitations, Toxicology Letters 112-113:467 (2000).

The technologies made possible by expression profiling and the DNA and polypeptide tools upon which they rely are now well-established. The technical literature recognizes not only the prevalence of these technologies, but also their unprecedented advantages in drug development, testing and safety assessment. One of these techniques is toxicology testing, used in both drug development and safety assessment. Toxicology testing is now standard practice in the pharmaceutical industry. See, *e.g.*, John C. Rockett, et al., Differential gene expression in drug metabolism and toxicology: practicalities, problems, and potential, Xenobiotica 29(7):655, 656 (1999):

Knowledge of toxin-dependent regulation in target tissues is not solely an academic pursuit as much interest has been generated in the pharmaceutical industry to harness this technology in the early identification of toxic drug candidates, thereby shortening the developmental process and contributing substantially to the safety assessment of new drugs.

To the same effect are several other scientific publications, including Emile F. Nuwaysir, et al., Microarrays and Toxicology: The Advent of Toxicogenomics, Molecular Genesis 24:153 (1999); Sandra Steiner and N. Leigh Anderson, *supra*.

Nucleic acids useful for measuring the expression of whole classes of genes are routinely incorporated for use in toxicology testing. Nuwaysir et al. describes, for example, a Human ToxChip comprising 2089 human clones, which were selected

... for their well-documented involvement in basic cellular processes as well as their responses to different types of toxic insult. Included on this list are DNA replication and repair genes, apoptosis genes, and genes responsive to PAHs and dioxin-like compounds, peroxisome proliferators, estrogenic compounds, and oxidant stress. Some of the other categories of genes include transcription factors, oncogenes, tumor suppressor genes, cyclins, kinases, phosphatases, cell adhesion and motility genes, and homeobox genes. Also included in this group are 84 housekeeping genes, whose hybridization intensity is averaged and used for signal normalization of the other genes on the chip.

See also Table 1 of Nuwaysir et al. (listing additional classes of genes deemed to be of special interest in making a human toxicology microarray).

The more genes that are available for use in toxicology testing, the more powerful the technique. "Arrays are at their most powerful when they contain the entire genome of the species they are being used to study." John C. Rockett and David J. Dix, Application of DNA Arrays to Toxicology, Environ. Health Perspec.107:681, No. 8 (1999). Control genes are carefully selected for their stability across a large set of array experiments in order to best study the effect of toxicological compounds. See attached email from the primary investigator, Dr. Cynthia Afshari to an Incyte employee, dated July 3, 2000, as well as the original message to which she was responding. Thus, there is no expressed gene which is irrelevant to screening for toxicological effects, and all expressed genes have a utility for toxicological screening. This is true for both polynucleotides and polypeptides encoded by them.

There are numerous additional uses for the information made possible by expression profiling. Expression profiling is used to identify drug targets and characterize disease. See Rockett et al., *supra*. It also is used in tissue profiling, developmental biology, disease staging, etc. There is simply no doubt that the sequences of expressed human genes all have practical, substantial and credible real-world utilities, at the very least for expression profiling.

Expression profiling technology is also used to identify drug targets and analyze disease at the molecular level, thus accelerating the drug development process. For example, expression profiling is useful for the elucidation of biochemical pathways, each pathway comprising a multitude of component polypeptides and thus providing a pool of potential drug targets. In this manner, expression profiling leads to the optimization of drug target identification and a comprehensive understanding of disease etiology and progression.

There is simply no doubt that the sequences of expressed human polynucleotides and

polypeptides all have practical, substantial and credible real-world utilities, at the very least for biochemical pathway elucidation, drug target identification, and assessment of toxicity and treatment efficacy in the drug development process. Sandra Steiner and N. Leigh Anderson, *supra*, have elaborated on this topic as follows:

The rapid progress in genomics and proteomics technologies creates a unique opportunity to dramatically improve the predictive power of safety assessment and to accelerate the drug development process. Application of gene and protein expression profiling promises to improve lead selection, resulting in the development of drug candidates with higher efficacy and lower toxicity. The identification of biologically relevant surrogate markers correlated with treatment efficacy and safety bears a great potential to optimize the monitoring of pre-clinical and clinical trials.

In fact, the potential benefit to the public, in terms of lives saved and reduced health care costs, are enormous. Recent developments provide evidence that the benefits of this information are already beginning to manifest themselves. Examples include the following:

- In 1999, CV Therapeutics, an Incyte collaborator, was able to use Incyte gene expression technology, information about the structure of a known transporter gene, and chromosomal mapping location, to identify the key gene associated with Tangiers disease. This discovery took place over a matter of only a few weeks, due to the power of these new genomics technologies. The discovery received an award from the American Heart Association as one of the top 10 discoveries associated with heart disease research in 1999.
- In an April 9, 2000, article published by the Bloomberg news service, an Incyte customer stated that it had reduced the time associated with target discovery and validation from 36 months to 18 months, through use of Incyte's genomic information database. Other Incyte customers have privately reported similar experiences. The implications of this significant saving of time and expense for the number of drugs that may be developed and their cost are obvious.
- In a February 10, 2000, article in the *Wall Street Journal*, one Incyte customer stated that over 50 percent of the drug targets in its current pipeline were derived from the Incyte database. Other Incyte customers have privately reported similar experiences. By doubling the number of targets available to pharmaceutical researchers, Incyte genomic information has demonstrably accelerated the development of new drugs.

Because the rejections failed to address or consider the "well-established" utilities for the claimed invention in toxicology testing, drug development, and the diagnosis of disease, the rejections should be withdrawn regardless of their merit.

ii. The use of the claimed polypeptides for toxicology testing, drug discovery,

and disease diagnosis are practical uses that confer “specific benefits” to the public.

Even if, *arguendo*, toxicology testing, drug development and disease diagnosis (through expression profiling) are not well-established utilities (which expressly is not conceded), the claimed invention nonetheless has specific utility by virtue of its use in each of these techniques. There is no dispute that the claimed invention is in fact a useful tool in each of these techniques. That is sufficient to establish utility for both the polypeptides and the polynucleotides encoding them.

Nevertheless, the claimed invention is rejected on the grounds that it does not have a “specific utility” absent a detailed description of the actual function of the claimed protein or identification of a “specific” disease it can be used to diagnose or treat. Apparently relying on the Training Materials, the rejection is made based on a scientifically incorrect and legally unsupportable assertion that identification of the family or families of proteins, without more, does not satisfy the utility requirement. None of these grounds is consistent with the law.

a. A patent applicant can specify a utility without any knowledge as to how or why the invention has that utility.

It is settled law that how or why any invention works is irrelevant to determining utility under 35 U.S.C. § 101: “[I]t is not a requirement of patentability that an inventor correctly set forth, or even know, how or why the invention works.” *In re Cortright*, 165 F.3d, at 1359 (quoting *Newman v. Quigg*, 877 F.2d 1575, 1581, 11 USPQ2d 1340 (Fed. Cir. 1989)). *See also Fromson v. Advance Offset Plate, Inc.*, 720 F.2d 1565, 1570, 219 USPQ 1137 (Fed. Cir. 1983) (“[I]t is axiomatic that an inventor need not comprehend the scientific principles on which the practical effectiveness of his invention rests.”). It follows that the patent applicant need not set forth the particular functionality of the claimed invention to satisfy the utility requirement.

Practical, beneficial use, not functionality, is at the core of the utility requirement. *Supra* (introduction to § A). So long as the practical benefits are apparent from the invention without speculation, the requirement is satisfied. *Standard Oil Co. v. Montedison*, 664 F.2d 356, 374, 212 USPQ 327 (3d Cir. 1981); *see also Brana*, 51 F.3d at 1565. To state that a biological molecule might be useful to treat some unspecified disease is not, therefore a specific utility. *In re Kirk*, 376 F.2d 936, 945, 153 USPQ 48 (C.C.P.A. 1967). The molecule might be effective, and it might not.

However, unlike the synthetic molecules of *Kirk*, the claimed invention is **known** to be useful. It is not just a random sequence of speculative use. Because it is expressed in humans, a person of ordinary skill in the art would know how to use the claimed polypeptide sequences -- without any guesswork -- in toxicology testing, drug development, and disease diagnosis regardless of how the protein actually functions. The claimed invention could be used, for example, in a toxicology test to determine whether a drug or toxin causes any change in the expression of molecules involved in cancer, or reproductive or immunological disorders. Similarly, the claimed invention could be used to determine whether a specific medical condition, such as prostate cancer, affects the expression of PGAMP proteins, and, perhaps in conjunction with other information, serve as a marker for or to assess the stage of a particular disease or condition.

In fact, the claimed invention could be used in toxicology testing and diagnosis without **any** knowledge (although this is not the case here) of the protein: it could serve, for example, as a marker of a toxic response, or, alternatively, if levels of the claimed polypeptide remain unchanged during a toxic response, as a control in toxicology testing. Diagnosis of disease (or fingerprinting using expression profiles) can be achieved using arrays of numerous identifiable, expressed DNA sequences, or by two-dimensional gel analysis of the expressed proteins themselves, notwithstanding lack of any knowledge of the function of the proteins.

b. A patent applicant may specify a utility that applies to a broad class of inventions.

The fact that the claimed invention is a member of a broad class (such as DNA sequences or the proteins they encode expressed in humans) that includes sequences other than those claimed that also have utilities in toxicology testing, drug discovery, disease diagnosis, etc. does not negate utility. Practical utilities can be directed to classes of inventions, irrespective of function, so long as a person of ordinary skill in the art would understand how to achieve a practical benefit from knowledge of the class. *Montedison*, 664 F.2d at 374-75. The law has long assumed that inventions that achieve a practical use also achieved by other inventions satisfy the utility requirement. For example, many materials conduct electricity. Likewise, many different plastics can be used to form useful films. *Montedison*, 664 F.2d at 374-75; *Natta*, 480 F.2d at 1397. This is a general utility (practical films) that applies to a broad class of inventions

(plastics) which satisfies the utility requirement of 35 U.S.C. § 101.

Not all broad classes of inventions are, by themselves, sufficient to inform a person of ordinary skill in the art of the practical utility for a member of the class. Some classes may indeed convey too little information to a person of ordinary skill in the art. These may include classes of inventions that include both useful and nonuseful members. *See In re Ziegler*, 992 F.2d 1197, 1201, 26 USPQ2d 1600 (Fed. Cir. 1993). In some of these cases, further experimentation would be required to determine whether or not a member of the class actually has a practical use. *Brenner*, 383 U.S. at 534-35.

The broad class of steroids identified in *Kirk* is just such a class. It includes natural steroids (concededly useful) and man-made steroids, some of which are useful and some of which are not. Indeed, only a small fraction of the members of this broad class of invention may be useful. Without additional information or further experimentation, a person of ordinary skill in the art would not know whether a member of the class falls into the useful category or not. This could also be the case for the broad class of “plastic-like” polypropylenes in *Ziegler*, which includes many -- perhaps predominately -- useless members.

The PTO routinely issues patents whose utility is based solely on the claimed inventions’ membership in a class of useful things. The PTO presumably would issue a patent on a novel and nonobvious fishing rod notwithstanding the lack of any disclosure of the particular fish it might be used to catch. The standard being promulgated in the Guidelines and in particular as exemplified in the Training Materials, and being applied in the present rejection, would appear to warrant a rejection, however, on the grounds that the use of the fishing rod is applicable to the general class of devices used to catch fish.

The PTO must apply the same standard to the biotechnological arts that it applies to fields such as plastics and fishing equipment. *In re Gazave*, 379 F.2d 973, 977-78, 154 USPQ 92 (CCPA 1967) *quoting In re Chilowsky*, 299 F.2d 457, 461, 108 USPQ 321 (CCPA 1956) (“[T]he same principles should apply in determining operativeness and sufficiency of disclosure in applications relating to nuclear fission art as in other cases.”); *see also In re Alappat*, 33 F.3d 1526, 1566, 31 USPQ2d 1545 (Fed. Cir. 1994) (Archer, C.J., concurring in part and dissenting in part) (“Discoveries and inventions in the field of digital electronics are analyzed according to the aforementioned principles [concerning patentable subject matter] as any other subject matter.”).

Indeed, there are numerous classes of inventions in the biotechnological arts that satisfy the utility requirement.

Take, for example, the class of interleukins expressed in human cells of the immune system. Unlike the classes of steroids or plastic-like polypropylenes in *Kirk* and *Ziegler*, all of the members of this class have practical uses well beyond “throwaway” uses. All of them cause some physiological response (in cells of the immune system). All of the genes encoding them can be used for toxicology testing to generate information useful in activities such as drug development, even in cases where little is known as to how a particular interleukin works. No additional experimentation would be required, therefore, to determine whether an interleukin has a practical use. It is well-known to persons of ordinary skill in the art that there is no such thing as a useless interleukin.

Because all of the interleukins, as a class, convey practical benefit (much like the class of DNA ligases identified in the Training Materials), there is no need to provide additional information about them. A person of ordinary skill in the art need not guess whether any given interleukin conveys a practical benefit or how that particular interleukin works.

Another example of a class that by itself conveys practical benefits is the G protein-coupled receptors (“GPCRs”). GPCRs are well-known as intracellular signaling mediators with diverse functions critical to complex organisms. They perform these functions by binding to and interacting with specific ligands. They are targets of many current drug treatments, including anti-depressants, anti-histamines, blood pressure regulators, and opiates.

Newly-identified GPCRs are used intensively in the real-world, even in cases where neither the specific ligand that binds to the GPCR or the precise biological function of the GPCR is known. Newly identified GPCRs are used, for example, as toxicity controls for drug candidates known to bind other GPCRs. Because a person of ordinary skill in the art would know how to use any GPCR to achieve a practical benefit, even without any detailed or particular knowledge as to how it works, GPCRs as a class meet the utility requirement.

In fact, all isolated and purified naturally-occurring polynucleotide and polypeptide sequences which are expressible (i.e., which are not pseudogenes that are never expressed during any natural biological process) can be and are used in a real-world context as tools for toxicological testing, e.g., for drug discovery purposes. This utility applies to all sequences

actually expressed, yet in each case, the utility of the sequence is quite specific, e.g., insofar as it is used to detect its own specific complementary sequence in a sample containing many different sequences.

Prostate growth-associated membrane proteins, like interleukins, GPCRs and fishing rods, is a class that by itself conveys practical benefits. Unlike steroids and “plastic-like” polypropylenes, all of the claimed prostate growth-associated membrane proteins are expressed by humans, and all of them can be used as tools for toxicology testing. The claimed invention could be used, for example to determine whether a drug candidate affects the expression of prostate growth-associated membrane proteins in humans, how it does so, and to what extent. Just as there are no useless interleukins and GPCRs, there are no useless prostate growth-associated membrane proteins of the claimed invention. As these are practical, real-world uses, the application need not describe particular functionality or medical applications that would only supplement the utilities known to exist already.

- iii. **Because the use of prostate growth-associated membrane proteins in toxicology testing, drug discovery, and disease diagnosis are practical uses beyond mere study of the invention itself, the claimed invention has substantial utility.**

In addition to conferring a specific benefit on the public, the benefit must also be “substantial.” *Brenner*, 383 U.S. at 534. A “substantial” utility is a practical, “real-world” utility. *Nelson v. Bowler*, 626 F.2d 853, 856, 206 USPQ 881 (CCPA 1980).

The claimed invention’s use as a tool for toxicology testing is just such a practical, real-world use. Although the rejection is not expressly based on lack of practical utility, and/or ignores this basis for utility, as stated it is tantamount to a rejection based on the sequence being only a research tool, on the ground that the use of an invention as a tool for research is not a “substantial” use. Because the PTO’s rejection in this light assumes a substantial overstatement of the law, it must be withdrawn.

There is no authority for the proposition that use as a tool for research is not a substantial utility. In fact, the PTO issues patents for inventions whose only use is to facilitate research, such as DNA ligases. These are acknowledged by the PTO’s Training Materials themselves to be useful.

Only a limited subset of research uses are not “substantial” utilities: those in which the

only known use for the claimed invention is to be an **object** of further study, thus merely inviting further research. This follows from *Brenner*, in which the U.S. Supreme Court held that a process for making a compound does not confer a substantial benefit where the only known use of the compound was to be the object of further research to determine its use. *Id.* at 535. Similarly, in *Kirk*, the CCPA held that a compound would not confer substantial benefit on the public merely because it might be used to synthesize some other, unknown compound that would confer substantial benefit. *Kirk*, 376 F.2d at 940, 945 (“What appellants are really saying to those in the art is take these steroids, experiment, and find what use they do have as medicines.”). Nowhere do those cases state or imply, however, that a material cannot be patentable if it has some other beneficial use in research.

As used in toxicology testing, drug discovery, and disease diagnosis, the claimed invention has a beneficial use in research other than studying the claimed invention. It is a tool, rather than an object, of research. The claimed invention has numerous other uses as a research tool, each of which alone is a “substantial utility”. These include diagnostic assays (pages 33-36), drug screening (page 38), etc.

iv. Objective evidence corroborates the utilities of the claimed invention.

There is in fact no restriction on the kinds of evidence a Patent Examiner may consider in determining whether a “real-world” utility exists. Indeed, “real-world” evidence, such as evidence showing actual use or commercial success of the invention, can demonstrate conclusive proof of utility. *Raytheon v. Roper*, 220 USPQ2d 592 (Fed. Cir. 1983); *Nestle v. Eugene*, 55 F.2d 854, 856, 12 USPQ 335 (6th Cir. 1932). Indeed, proof that the invention is made, used or sold by any person or entity other than the patentee is conclusive proof of utility. *United States Steel Corp. v. Phillips Petroleum Co.*, 865 F.2d 1247, 1252, 9 USPQ2d 1461 (Fed. Cir. 1989).

Over the past several years, a vibrant market has developed for databases containing all expressed genes, in particular genes having medical and pharmaceutical significance such as the instant sequence. (Note that the value in these databases is enhanced by their completeness, but each sequence in them is independently valuable.) The databases sold by Applicants’ assignee, Incyte, include exactly the kinds of information made possible by the claimed invention, such as tissue and disease associations. Incyte sells its database containing the claimed sequence and millions of other sequences throughout the scientific community, including to pharmaceutical

companies who use the information to develop new pharmaceuticals.

B. The Patent Examiner failed to demonstrate that a person of ordinary skill in the art would reasonably doubt the utility of the claimed invention.

In addition to alleging a “specific” use for the claimed subject matter, a patent applicant must present proof that the claimed subject matter is in fact useful. *Brana*, 51 F.3d at 1565-66. The applicant need only prove a “substantial likelihood” of utility; certainty is not required. *Brenner*, 383 U.S. at 532.

The amount of evidence required to prove utility depends on the facts of each particular case. *In re Jolles*, 628 F.2d 1322, 1326, 206 USPQ 885 (CCPA 1980). “The character and amount of evidence may vary, depending on whether the alleged utility appears to accord with or to contravene established scientific principles and beliefs.” *Id.* Unless there is proof of “total incapacity,” or there is a “complete absence of data” to support the applicant’s assertion of utility, the utility requirement is met. *Brooktree Corp. v. Advanced Micro Devices, Inc.*, 977 F.2d 1555, 1571, 24 USPQ2d 1401 (Fed. Cir. 1992); *Envirotech*, 730 F.2d at 762.

A patent applicant’s assertion of utility in the disclosure is presumed to be true and correct. *In re Cortright*, 165 F.3d at 1356; *Brana*, 51 F.3d at 1566. If such an assertion is made, the Patent Office bears the burden in the first instance to demonstrate that a person of ordinary skill in the art would reasonably doubt that the asserted utility could be achieved. *Ids.* To do so, the PTO must provide evidence or sound scientific reasoning. *See Langer*, 503 F.2d at 1391-92. If and only if the Patent Office makes such a showing, the burden shifts to the applicant to provide rebuttal evidence that would convince the person of ordinary skill that there is sufficient proof of utility. *Brana*, 51 F.3d at 1566. The Revised and final Utility Guidelines are in agreement with this procedure. *See Revised and final Guidelines at ¶¶ 3-4.*

The issue of proof often arises in the chemical and biotechnological arts when the patentee asserts a utility for a claimed chemical compound based on its homology or similarity to another compound having a known, established utility. In such cases, the applicant can demonstrate “substantial likelihood” of utility by demonstrating a “reasonable correlation” between the utility -- not the function -- of the known compound and the compound being claimed. *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1565, 39 USPQ2d 1895 (Fed. Cir. 1996). Accordingly, under *Brana*, the Patent Office must accept the asserted utility unless it can show that a person of

ordinary skill in the art would reasonably doubt that a "reasonable correlation" exists.

C. By requiring the Patent Applicant to assert a particular or unique utility, the Patent Examination Utility Guidelines and Training Materials applied by the Patent Examiner misstate the Law.

The Training Materials, which direct the Examiners regarding how to apply the Utility Guidelines, address the issue of specificity with reference to two kinds of asserted utilities:

"specific" utilities which meet the statutory requirements, and "general" utilities which do not.

The Training Materials define a "specific utility" as follows:

A [specific utility] is *specific* to the subject matter claimed. This contrasts to *general* utility that would be applicable to the broad class of invention. For example, a claim to a polynucleotide whose use is disclosed simply as "gene probe" or "chromosome marker" would not be considered to be specific in the absence of a disclosure of a specific DNA target. Similarly, a general statement of diagnostic utility, such as diagnosing an unspecified disease, would ordinarily be insufficient absent a disclosure of what condition can be diagnosed.

The Training Materials distinguish between "specific" and "general" utilities by assessing whether the asserted utility is sufficiently "particular," *i.e.*, unique (Training Materials at p.52) as compared to the "broad class of invention." (In this regard, the Training Materials appear to parallel the view set forth in Stephen G. Kunin, Written Description Guidelines and Utility Guidelines, 82 J.P.T.O.S. 77, 97 (Feb. 2000) ("With regard to the issue of specific utility the question to ask is whether or not a utility set forth in the specification is *particular* to the claimed invention.")).

Such "unique" or "particular" utilities never have been required by the law. To meet the utility requirement, the invention need only be "practically useful," *Natta*, 480 F.2d 1 at 1397, and confer a "specific benefit" on the public. *Brenner*, 383 U.S. at 534. Thus incredible, "throw-away" utilities, such as trying to "patent a transgenic mouse by saying it makes great snake food" do not meet this standard. Karen Hall, Genomic Warfare, *The American Lawyer* 68 (June 2000) (quoting John Doll, Chief of the Biotech Section of USPTO).

This does not preclude, however, a general utility, contrary to the statement in the Training Materials where "specific utility" is defined (page 5). Practical real-world uses are not limited to uses that are unique to an invention. The law requires that the practical utility be "definite," not particular. *Montedison*, 664 F.2d at 375. Appellant is not aware of any court that has rejected an assertion of utility on the grounds that it is not "particular" or "unique" to the

specific invention. Where courts have found utility to be too "general," it has been in those cases in which the asserted utility in the patent disclosure was not a practical use that conferred a specific benefit. That is, a person of ordinary skill in the art would have been left to guess as to how to benefit at all from the invention. In *Kirk*, for example, the CCPA held the assertion that a man-made steroid had "useful biological activity" was insufficient where there was no information in the specification as to how that biological activity could be practically used. *Kirk*, 376 F.2d at 941.

The fact that an invention can have a particular use does not provide a basis for requiring a particular use. See *Brana, supra* (disclosure describing a claimed antitumor compound as being homologous to an antitumor compound having activity against a "particular" type of cancer was determined to satisfy the specificity requirement). "Particularity" is not and never has been the *sine qua non* of utility; it is, at most, one of many factors to be considered.

As described *supra*, broad classes of inventions can satisfy the utility requirement so long as a person of ordinary skill in the art would understand how to achieve a practical benefit from knowledge of the class. Only classes that encompass a significant portion of nonuseful members would fail to meet the utility requirement. *Supra* § A.2.b (*Montedison*, 664 F.2d at 374-75).

The Training Materials fail to distinguish between broad classes that convey information of practical utility and those that do not, lumping all of them into the latter, unpatentable category of "general" utilities. As a result, the Training Materials paint with too broad a brush. Rigorously applied, they would render unpatentable whole categories of inventions heretofore considered to be patentable, and that have indisputably benefitted the public, including the claimed invention. See *supra* § A.2. Thus the Training Materials cannot be applied consistently with the law.

D. To the extent the rejection of the claims under 35 U.S.C. § 112, first paragraph, is based on a lack of an enabling disclosure which would allow one of skill in the art to make and/or use the claimed invention, or is based on a lack of utility under 35 U.S.C. § 101, it must be withdrawn as well.

The rejections set forth in the Office Action are based on the assertions discussed above, i.e., that the claimed invention lacks patentable utility, or on an alleged lack of enablement which would allow one of skill in the art to make and/or use the claimed invention. To the extent that the rejection under § 112, first paragraph, is based on the improper allegation of lack of

patentable utility under § 101, it fails for the same reasons cited above. Similarly, since the claimed invention has a specific and substantial asserted utility, or a well established utility, one of skill in the art **would** know how to make and/or use the claimed invention **without** undue experimentation. Therefore, the rejections under 35 U.S.C. § 112 should be withdrawn.

CONCLUSION

In light of the above amendments and remarks, Applicants submit that the present application is fully in condition for allowance, and request that the Examiner withdraw the outstanding rejections. Early notice to that effect is earnestly solicited.

If the Examiner contemplates other action, or if a telephone conference would expedite allowance of the claims, Applicants invite the Examiner to contact the undersigned at (650) 843-7352 or (650) 621-8581.

Applicants believe that no fee is due with this communication. However, if the USPTO determines that a fee is due, the Commissioner is hereby authorized to charge Deposit Account No. 09-0108. This form is enclosed in duplicate.

Respectfully submitted,

INCYTE GENOMICS, INC.

Date: May 9, 2001

Terry Lo

Terence P. Lo, Ph.D.

Limited Recognition (37 C.F.R. § 10.9(b)) attached

Direct Dial Telephone: (650) 621-8581

Date: 09 May 2001

Richard C. Ekstrom

Richard C. Ekstrom

Reg. No. 37,027

Direct Dial Telephone: (650) 843-7352

3160 Porter Drive
Palo Alto, California 94304
Phone: (650) 855-0555
Fax: (650) 849-8886

VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS:

Claims 2 and 28 have been amended as follows:

2. (Three Times Amended) [A purified] An isolated polypeptide comprising an amino acid sequence selected from the group consisting of:

a) a [polypeptide] naturally-occurring amino acid sequence having at least 90% amino acid sequence identity to SEQ ID NO:1 [that binds specifically with an anti-PGAMP-1 antibody], and

b) a [polypeptide] naturally-occurring amino acid sequence having at least 90% amino acid sequence identity to SEQ ID NO:2 [that binds specifically with an anti-PGAMP-2 antibody].

28. (Amended) A substantially purified polypeptide comprising a fragment of the polypeptide of claim 1, wherein said fragment consists of at least 15 conti[n]guous amino acids of SEQ ID NO:1, and wherein said fragment binds specifically with an anti-PGAMP-1 antibody.